Clinical Study Report Synopsis for Public Disclosure

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The study listed may include information about approved and non-approved uses, doses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Patients should always seek medical advice before making any decisions on their treatment. Healthcare professionals should always refer to the specific prescribing information approved for the patient's country or region.

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2. SYNOPSIS

Study Title	A prospective, open-label, multicenter, repeat-dose trial to investigate the safety and efficacy of NT 201, free of complexing proteins, in the treatment of glabellar frown lines
Name of Finished Product	Botulinum Neurotoxin 201 [NT 201]
Name of Active Ingredient	NT 201 containing 100 mouse LD_{50}-units NT 101 (*Clostridium botulinum* neurotoxin type A [150 kilodalton (kDa)] free of complexing proteins)
Phase of Development	Phase 3
Publication (reference)	None
Objective	To investigate the safety and efficacy of NT 201 in repeat-dose treatment of glabellar frown lines.
Coordinating Investigators	[redacted] Coordinating Investigator Germany ("Leiter der Klinischen Prüfung" according to German Drug Law). [redacted] Coordinating Investigator North America.
Number of study centers	26 centers in the United States, Canada and Germany who participated in one of the following feeder studies in this program, i.e., MRZ 60201-0520/1, MRZ 60201-0527/1, MRZ 60201-0724/1 and MRZ 60201-0741/1.
Study period	18 Jun 2007 (first subject first visit). 28 Dec 2009 (last subject last visit).
Number of subjects (planned and analyzed)	Planned: approximately 880 subjects (approximately 370 subjects of feeder studies MRZ 60201-0520/1 and MRZ 60201-0527/1 and approximately 510 subjects from studies MRZ 60201-0724/1 and MRZ 60201-0741/1. Analyzed: 796 subjects (Full Analysis Set [FAS]).

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Methodology	This was a prospective, multicenter, open-label, non-control group design Phase 3 clinical study. Subjects with moderate to severe glabellar frown lines at maximum frown who completed participation in one of the studies in this program, i.e., MRZ 60201-0520/1, MRZ 60201-0527/1, MRZ 60201-0724/1, or MRZ 60201-0741/1 were eligible to participate in this repeat-dose study. Each subject received an intramuscular [i.m.] injection of 20 Units [U] NT 201 on Visit 1 (Day 0 of Cycle 1), evenly divided to five injection points. Re-injections could be performed on Day 0 of a subsequent cycle up to eight cycles (one cycle ≥ 85 days).
Diagnosis and main criteria for inclusion	Diagnosis: Moderate to severe glabellar frown lines. Inclusion criteria at Screening: Females and males fulfilling the following criteria were eligible: • Moderate to severe glabellar frown lines at maximum frown as assessed by the investigator according to Facial Wrinkle Scale [FWS] (severity score of 2 or 3). • Completion of one study in this program (i.e., MRZ 60201-0520/1, MRZ 60201-0527/1, MRZ 60201-0724/1 or MRZ 60201-0741/1) within 45 days before Screening. • Stable medical condition. • Age 18 or over. Eligibility criteria for re-injections in Cycle 2 (completers of studies MRZ 60201-0724/1 and MRZ 60201-0741/1) and in Cycles 2 to 8 (completers of studies MRZ 60201-0520/1 and MRZ 60201-0527/1), respectively: • Relapse to moderate or severe glabellar frown lines at maximum frown on FWS as assessed by the investigator. • Lack of any condition or situation that in the investigator's opinion may put the subject at

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	significant risk or may interfere significantly with the subject's participation in the study.
Investigational product	**Investigational Medicinal Product** NT 201 containing 100 mouse LD_{50}-units NT 101 (*Clostridium Botulinum* neurotoxin type A [150 kDa] free of complexing proteins) **Dose** A dose of 20 U NT 201 per treatment cycle was administered. One treatment consisted of administration to five injection sites in equal aliquots. **Route of administration** • Point A: One injection in the procerus muscle at the crossing of two lines connecting point B and the contralateral caruncle. • Point B: One injection on each side in the central part of the corrugator muscle approximately 1 cm above the orbital rim on an imaginary line drawn vertically from the caruncle. • Point C: One injection on each side in the middle part of the corrugator muscle at least 1.5 cm above the orbital rim on an imaginary line drawn vertically from the midpupillary line.
Reference product	Not applicable.
Duration of treatment per subject	The maximum treatment duration per subject was 24 months (for completers of studies MRZ 60201-0520/1 and MRZ 60201-0527/1) or 6 months/ 1-2 cycles (for completers of studies MRZ 60201-0724/1, and MRZ 60201-0741/1).
Criteria for evaluation	**Safety:** • Incidence of adverse events [AEs]. • Incidence of AEs of special interest [AESIs]. • Laboratory evaluations: Clinical biochemistry and hematology at Screening and end of study [EOS] and at least every 12 months for completers of studies MRZ 60201-0520/1 and

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	MRZ 60201-0527/1. • Botulinum Neurotoxin type A antibody tests (fluorescence immunoassay [FIA-AB] and, if positive, subsequent hemidiaphragm assay [HDA]) at Screening and 30 days after treatment. • Vital signs (pulse rate, blood pressure) at all visits. • Physical examination at Screening and EOS and at least every 12 months for completers of studies MRZ 60201-0520/1 and MRZ 60201-0527/1. • Concomitant medications at all visits. • Concomitant treatments at all visits.
	Efficacy: • Percentage of responders at maximum frown (defined as score 'none' or 'mild') at each visit as assessed by the investigator according to FWS. • Percentage of responders at rest at each visit as assessed by the investigator according to FWS. • Percentage of responders at maximum frown and at rest at each visit by subject's assessment on a 4-point scale. • Subject's assessment on the 6-point Likert type scale. • Time to onset of treatment effect.
Statistical methods	The presentation of data for this study was stratified by the treatment dose that the subjects had received during the previous studies. The term "treatment" was used, which actually describes the pre-treatment dose the subject received in the previous study. In detail, the following groups (pre-treatments) were distinguished: • Placebo – 20 U NT 201. • 10 U – 20 U NT 201. • Continuous 20 U NT 201. • 30 U – 20 U NT 201.

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	Safety analyses: Safety analyses were based on the FAS that consisted of all subjects who were successfully screened for the study (Informed Consent signed) and had at least one study drug application during this study. AEs, AESIs, concomitant medications and treatments were displayed using frequency tables. Antibody test results were presented using frequency tables over time. Continuous safety parameters were analyzed using descriptive statistical methods. **Efficacy analyses:** All efficacy analyses were based on the FAS and per protocol set [PPS]. Efficacy variables were analyzed over time using descriptive summary statistics. Subgroup analyses were done for gender, age group, and ethnicity. All statistical evaluations were explorative. When at least 300 subjects had completed an observation period of at least 12 months, an One-Year Evaluation was performed on all safety and efficacy data of all completed treatment cycles of all study subjects which were available at that time.

Safety Results

During the study period, 361 (45.4%) subjects experienced at least one treatment-emergent AE [TEAE]. Overall, 50 (6.3%) subjects experienced a TEAE related to the study drug, as assessed by the investigator, most of those with mild (37 [4.6%]) or moderate (11 [1.4%]) intensity. The most common drug-related TEAE was headache, observed in 28 (3.5%) subjects. The small number of related TEAEs indicates a good tolerance of the evaluated drug.

Overall, nine (1.1%) subjects experienced at least one TEAE of special interest, four (0.5%) subjects with facial paresis (reported terms: ‘bilateral brow ptosis’ [in two subjects], ‘facialis paresis’ and ‘right brow ptosis’), two (0.3%) subjects with eyelid ptosis, and one subject (0.1%) each with eyelid function disorder, muscular weakness (reported term: ‘left arm weakness’) and pneumonia aspiration. In five (0.6%) subjects, these events were related to the study drug.

Overall, 29 (3.6%) subjects experienced a serious TEAE. None of the serious TEAEs were related to the study drug. 19 serious TEAEs were of severe intensity. No fatal AEs were reported. All serious TEAEs resolved except one which resolved with sequelae ([redacted]

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[redacted]), and one which was recovering/resolving ([redacted]).

Overall six (0.7%) subjects experienced TEAEs which led to discontinuation from the study (documented as the 'main reason' for premature termination).

The continent subgroup analyses showed higher incidences of TEAEs in Europe as compared to North America (69.5% versus 38.4%). There were no obvious differences in the TEAE profile between male and female subjects and subjects ≤ 50 years and subjects > 50 years. The incidence was higher in white subjects (49.0%) compared to non-white subjects (26.0%). However, these analyses results have to be interpreted with caution due to the different group sizes.

Generally, the incidence of TEAEs remained fairly constant in each subsequent cycle, indicating a stable safety pattern after repeated dosing. There was no cumulative effect observed with increasing numbers of injections received. There were no new unexpected events occurring, and the TEAE profile was consistent with the one observed in previous studies. AESIs were reported in Cycles 1, 2 and 3 only. There was no rise in adverse events compared to previous studies. The incidence rate, cumulated overall for subjects with events in 1,000 treatment cycles, was constant for all cycles.

Evaluation of laboratory parameters and vital signs showed no relevant changes in mean values or abnormal findings in any treatment group during the course of the study and did not raise any safety concerns. Only one subject who was pre-treated with Botulinum toxin before the study entry, tested positive for HDA antibodies (at Screening). However, the antibody sample was reported to be stored incorrectly, and the subject was tested negative after his first and only treatment during the study (Cycle 1 Evaluation Visit).

The overall incidences of TEAEs were lower in the Final Evaluation compared to the One-Year Evaluation (Final Evaluation: Overall TEAEs in 45.4% [361 subjects]; One-Year Evaluation: Overall TEAEs in 68.1% [236 subjects]). This confirms that during repeated injections, no increase in the incidence of TEAEs was observed. Likewise, no increase in the occurrence of SAEs, related TEAEs or severe TEAEs was detected. With regards to the PT pattern, the observations are generally in line with those made during the One-Year Evaluation. Regarding the continent subgroup analyses, it was shown that the overall incidences of TEAEs in the Final Evaluation were higher in Europe than in North America. This observation is different to the One-Year Evaluation which could be due to the increased number of subjects from North America who only had a low number of treatment cycles (up to two cycles as per protocol). Effects by continent were expected to a certain extent during this study and seemed to be evident during the One-Year Evaluation. However, for the final analysis it turned out that the effects might not depend on continent but on the feeder studies. Subjects by feeder studies were not analysed separately in this study since this was not part of the protocol.

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Efficacy Results

Responder rates as assessed by the investigator at maximum frown according to FWS at Day 30 (Evaluation Visit) ranged from 79.1% to 89.6% in the eight evaluated cycles. The responder rates were stable during Cycles 1 to 7 at around 80% (79.1% to 82.7%). The responder rate was slightly higher in Cycle 8 with 89.6% (however, this could be due to the smaller case numbers and due to the fact that this was the last possible cycle and subjects had not to wait for a new injection.). Responder rates as assessed by the subject at maximum frown according to the 4-point scale were higher at Day 30 (ranging from 86.2% to 93.8% in the eight cycles) and lower at the Control Visit (ranging from 31.2% to 60.4%) than those assessed by the investigator according to FWS.

Responder rates as assessed by the investigator at rest according to FWS (ranging from 77.0% to 87.5% in the eight cycles) at Day 30 were still high at the Control Visit (ranging from 57.0% to 83.3%), due to the different baseline situations at maximum frown in contrary to baseline at rest. Responder rates as assessed by the subject at rest according to the 4-point scale (ranging from 67.0% to 77.1% in the eight cycles at Day 30 and from 35.1% to 58.3% at the Control Visit) were lower than those assessed by the investigator according to FWS.

Responder rates as assessed by the investigator at maximum frown according to FWS were higher in subjects aged ≤ 50 years, in female subjects, and in non-white subjects. However, these differences have to be interpreted with caution due to the small number of subjects in one of either subgroup.

The number and percentage of subjects with deep glabellar frown lines as assessed by the subject on the 4-point scale at maximum frown and at rest lessened between Injection and Evaluation Visits and enlarged again in the time between the Evaluation and Control Visits in all cycles.

A similar trend was observed in the subject's assessments on the 6-point Likert type scale regarding the number of subjects with very deep glabellar frown lines both at maximum frown and at rest.

In all cycles, the treatment effect had occurred in approximately 50% of subjects three days after injection and in 90% one week after the injection.

The time between injections was nearly constant; there were no clinically significant signs for decreasing effectiveness over time.

Throughout the whole study period, the responder rates were continuously high and constant over all cycles, and a stable and enduring treatment effect was obvious, even with repeated injections. Treatment results could be reproduced over several cycles. These observations are in line with those made during the One-Year Evaluation.

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Conclusion

Repeated injections with NT 201 can be considered as effective, safe and well-tolerated in the treatment of glabellar frown lines.

Date of Report: 30 June 2010